REMARKS

Claims 2-4, 8-10, and 13-25 are in the application.

The specification has been carefully reviewed and amended to correct minor typographical errors. In addition, sequence identifiers have been added where appropriate in the specification. On review of Table 2, it was determined that one of the primer sequences had been inadvertently duplicated in preparing the English language translation of the specification, based on the order of sequences in the sequence listing and the corresponding entry in the Chinese international application. The primer sequence has been corrected in Table 2 on this basis. Further, the specification has been amended to include express antecedent basis on page 5 for claim 7. Since claim 7 was part of the original disclosure, this amendment raises no issue of new matter.

The claims have been amended to more particularly point out and distinctly claim applicants' invention. Independent claims 1 and 7 have been cancelled in favor new independent claims 13 and 22, which incorporate the subject matter of cancelled independent claims revised for additional clarity. Claims 5-7 and 11-12, drawn to non-elected subject matter, have been cancelled without prejudice to presentation in a subsequent continuing application. New dependent claims 15-22 relate to specific criteria for identifying polyepitope chimeric gene expression libraries desirable for subsequent screening of individual clones within the libraries such as disclosed on page 10 of the specification.

The amendments are fully supported by the application as filed, and introduce no new matter.

Objections to the Specification

The Examiner has objected to the disclosure because there are no sequence identifier numbers for all the sequences in the specification, such as at page 29, Table 1, and has required correction. This objection is respectfully traversed, and reconsideration and withdrawal of the objection are respectfully requested as applicable to the amended specification. Applicants have reviewed the specification, and inserted sequence identifier numbers where appropriate. Reconsideration and withdrawal of the objection to the disclosure as applicable to the amended specification are respectfully requested for this reason.

The Examiner notes that she has not checked the specification to the extent necessary to determine the presence of all possible minor errors, and has requested applicants' cooperation in correcting any errors of which applicants may become aware in the specification. Responsive to the Examiner's request, the specification has been carefully reviewed, and all minor errors encountered have been corrected by amendment.

The Examiner has further objected to the specification as failing to provide proper antecedent basis for the claimed subject matter, citing 37 CFR 1.75(d) (1) and MPEP ¶ 608.01(o). In particular, the Examiner states that claim 7 lacks antecedent basis or support or is inconsistent with the disclosed method, citing page 5 of the instant specification, and has required correction. This objection is respectfully traversed, and reconsideration and withdrawal of the objection are respectfully requested as applicable to the amended specification and claims. The specification has been amended to provide express antecedent basis for claim 7.

Alleged Lack of Written Description

Claims 1-4 and 7-10 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, on the ground that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested as applicable to the amended claims.

The Examiner states that the specification fails to provide an adequate written description of the claimed method utilizing gene vaccine components of such scope particularly a library of random gene sequences. In particular, the Examiner notes that the specification describes a method of making a polyepitopic chimeric gene vaccine obtained from the single organism, *Plasmodium falciparum*, and that other than this single embodied organism, no other organism has been shown to produce polyepitopic chimeric gene vaccines. Further, the Examiner states that the disclosure does not indicate that the single embodied organism can be applied to any type of organism, nor does the disclosure disclose which nor how the different epitopes in the numerous

epitopes of an organism can be derived to produce the polyepitopic chimeric gene vaccines.

The Examiner asserts that in vaccine formation there is the issue of where the combination of more epitopes creates many possibilities thus, making it impractical to assemble or construct library as used as a vaccine. The Examiner further states that it is impractical to assemble and construct polyepitopic gene vaccines let alone a library because it is complicated, costly and requires much work. The Examiner also states that more importantly, an answer as to how to effectively design polyepitope genes and overcome the variability of pathogens is required for the development of gene vaccines. (citing as an example, Li M. et al. Chin. Med. J. Engl.), 112 (8), 691-7, particularly the paragraph bridging pages 691—670.). The Examiner observes that the life cycle of *Plasmodium falciparum* which causes malignant malaria severely affecting human health is complicated and comprises four stages comprising asexual reproduction and sexual reproduction in humans and sexual reproduction and sporogony in mosquitoes. The Examiner reviews the exoerythrocytic (liver) and erythrocytic stages in humans as well as the gametocyte and sporozoite stages in mosquitoes, and further observes that such complex biological traits cause *Plasmodium falciparum* to have highly variable response against the immunoprotection of the host and drugs. The Examiner asserts that it is not apparent how the different length ranges for the numerous different organisms can be ascertain based only on the single species, *Plasmodia falciparum,* given that the same organism in different species such as, for example, humans are different. The Examiner further states that it is well-known in the art that under representation or overrepresentation of these different size ranges may not produce the epitope essential for vaccine formation. The Examiner helpfully suggests that applicants recite that the polyepitopic chimeric gene is obtained from *Plasmodium falciparum*.

In response to the Examiner's suggestion, applicants have added new claims addressed expressly to a method for use in constructing polyepitopic chimeric gene libraries from *Plasmodia falciparum*, noting however that original claim 10 limits the antigen of interest to antigens of *Plasmodia falciparum*.

Nevertheless, applicants respectfully submit that the rejection entered 35 USC 112, first paragraph, for an alleged lack of written description is not correct and should be withdrawn with respect to the claims as amended. The presently claimed invention is

drawn to a method for preparing polyepitope chimeric gene vaccines, not to such a gene vaccine itself. The products of the method are claimed in presently withdrawn claims 5, 6, 11 and 12. The Examiner identifies the difficulties in engineering an effective polyepitope gene vaccine. However, it is just such difficulties that the presently claimed method is intended to overcome, and its success in doing so is an indicia of its patentability. As the Examiner acknowledges, it is particularly difficult to construct a library of polyepitope chimeric gene vaccines in the case of a difficult organism such as *Plasmodia falciparum* which grows through four separate life stages. Applicants' success in doing so, as evidenced by the examples in the applicants' disclosure, shows the strength of the presently claimed method. Applicants' method is of general application, and is not in any way restricted to epitopes of antigens produced by any specific organism, such as *Plasmodia falciparum*. The method is of broad application, and the epitopes employed to prepare polyepitope chimeric gene vaccines can be obtained from antigens related to other infectious diseases, as well as tumor or autoimmune diseases (claim 8). Applicants' exemplification of their method using a particularly difficult organism is an unmistakable indication that they were in possession of the invention claimed at the time the present application was filed. Applicants respectfully contend that the Examiner has not carried her burden of showing that subject matter of the presently amended claims is not adequately described. In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996). The rejection entered under 35 U.S.C. 112, first paragraph, for lack of written description, should be withdrawn for this reason.

Rejection on Formal Grounds

Claims 1-4 and 7-10 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested as applicable to the amended claims.

The Examiner states that the expression “the corresponding length ranges” in claim 1 step (d) is a non-sequitur. The Examiner also states that it is not clear as to the manner by which the library is in said corresponding length ranges. The Examiner also

states that the expression "high diversity" in step (e), claim 1 is a non-sequitur, as well as the term “the immunogenicity” in step (f), claim 1.

The Examiner also opines that the term “high” modifying immunogenicity in claim 1 is a relative term which renders the claim indefinite. The Examiner explains that the term “high” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner also states that it is not clear as to what would be considered a high immunogenic member of a gene library.

Further, the Examiner states that the term "high" modifying "diversity" in claim 7 is similarly a relative term which renders claim 7 indefinite.

The Examiner also states that it is not clear as to the steps which are to be included or precluded by the scope of immunochemistry methods.

With respect to claim 1 step (e), the Examiner states that it is unclear what detection method is intended and the difference between the diversity of step (e) and the step (d) diversity which is created by difference in length.

The Examiner finds claim 1, step (g) to be unclear, especially in the absence of positive support or showing in the disclosure as to how this step is accomplished.

The Examiner also finds claim 7 to be indefinite as to step (d), in that the claim appear to include a term that is a square.

In response to the Examiner's rejection, independent claim 1 has been rewritten as new claim 13 and independent claim 7 has been rewritten as new claim 23 to address the various informalities identified by the Examiner. Applicants have retained the wording "high diversity" because one of ordinary skill in the art reading the present specification would understand the meaning of this wording. If one of ordinary skill in the art would reasonably understand the claim when read in the context of the specification, the claim satisfies the second paragraph definiteness requirement of 35 U.S.C. § 112. Miles Lab., Inc. v. Shandon, Inc., 997 F.2d 870, 875 (Fed. Cir. 1993); Union Pac. Res. Co. v. Chesapeake Energy Corp., 236 F.3d 684, 692 (Fed. Cir. 2001). In the paragraph bridging pages 10 and 11 of the specification, applicants disclose that the preferred range for the diversity of the polyepitope gene libraries to be greater than 85%. Thus, it is respectfully asserted that the Examiner has not established why one of ordinary skill in the art, reading claims employing this term, would not reasonably understand the scope

of the relative term "high" as applied to the diversity of the polyepitope gene libraries of the present invention. Similarly, applicants have retained the wording "high" as applied to the immunogenicity of the polyepitope gene libraries in dependent claim 15 because this expression would be understood by one of ordinary skill in the art in the context of applicants' disclosure, which includes examples employing two different commonly used methods of assessing immunogenicity, namely, the extent to which antibodies are produced (Example 4) and the activation of T-cells and production of cytokines (Example 6).

Rejection for Alleged Anticipation

Claims 1-4 and 7-10 stand are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al., Chinese J of Biochemistry (Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao) (1999), 15(6), 974-977 ("Lin et al."). This rejection is respectfully traversed, and reconsideration and withdrawal of the rejection are respectfully requested as applicable to the amended claims.

The Examiner states that Lin et al. discloses throughout the article, such as in the abstract that with the isocaudamers which have different recognition sequences and produce compatible cohesive ends, chimeric multi-epitope *Plasmodium falciparum* DNA vaccines including the multiplication of the single copy epitope and the tandem linkage of different kinds of epitopes were flexibly constructed. The Examiner further states that a specific B-cell response was detected by ELISA by Lin et al. after the immunization of BALB/c mice with the chimeric antigen, which demonstrated the usefulness of this strategy of constructing multi-epitope DNA vaccines. The Examiner concludes that the specific method steps of Lin using specific components fully meet the claimed method using broad components in the method. The Examiner further notes that applicants are required by 37 CFR 1.56 to submit information that may be material to patentability of the instant application since Lin et al. seems to be co-authored by one of the inventors, citing MPEP 704.12 (a).

The Examiner's conclusion is not correct. Lin does not identically disclose applicants' presently claimed invention.

Anticipation under § 102 requires strict identity. "Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to

anticipate the claim." Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997). "Every element of the claimed invention must be literally present, arranged as in the claim." Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Lin does not disclose a number of the limitations of independent claims 13 and 22, and thus cannot anticipate the presently claimed invention.

While Lin discloses the use of isocaudamers having different recognition sequences to produce chimeric multi-epitope *Plasmodium falciparum* DNA vaccines, there is no disclosure of randomly assembling polyepitope chimeric genes with different lengths from the nucleic acid molecules encoding randomly combined bi-epitopes as is required by step (c) of each independent claim. Further, Lin does not disclose isolating polyepitope chimeric genes into a plurality of different length ranges, purifying and amplifying the isolated polyepitope chimeric genes, subcloning the purified and amplified polyepitope chimeric genes into expression vectors, or transforming prokaryotic hosts with the expression vectors to obtain polyepitope chimeric gene expression libraries, the expression libraries corresponding to different length ranges into which the polyepitope chimeric gene libraries were isolated. Further, Lin does not disclose assessing the diversity of the polyepitope chimeric genes in the expression libraries, and selecting at least one polyepitope chimeric gene library based on diversity for use in preparing chimeric gene vaccines. In addition, Lin does not disclose immunizing animals with the polyepitope gene expression libraries to provide expression products of the polyepitope chimeric genes. Nor does Lin disclose detecting the immunogenicity of the expression products of the polyepitope chimeric genes. Lin does not disclose selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope chimeric gene expression libraries and the immunogenicity of the expression products of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries. Finally, Lin does not disclose screen the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines.

Because Lin does not expressly or inherently disclose at least one step of the presently claimed method, Lin cannot and does anticipate that invention. Reconsideration and withdrawal of the rejection entered under 35 U.S.C. 102(b) over Lin are respectfully requested for this reason.

Nor does Lin render the presently claimed invention obvious. There is no teaching, suggestion or motivation in Lin to, *inter alia*, randomly assemble the nucleic acids molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths, nor to isolate the polyepitope chimeric genes into a plurality of different length ranges, nor to clone the polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, nor to assess the diversity of those libraries. Thus, Lin would not render the presently claimed invention obvious to one or ordinary skill in the art at the time the invention was made.

Rejection for Alleged Obviousness

Claims 1-4 and 7-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,026,443 ("Sette et al.") or U.S. Patent 6,602,510 ("Fikes et al.") in view U.S. Patent 6,291,214 ("Richards et al.") or applicants' admission of known prior art. This rejection is respectfully but strenuously traversed, and reconsideration and withdrawal of the rejection are respectfully requested as applicable to the amended claims.

Sette et al. identifies and prepares human papilloma virus ("HPV") epitopes and epitope-based vaccines to HPV. The Examiner notes that Sette et al. disclose, among other things, a vaccine comprising a minigene that encodes a polyepitopic peptide, such as a minigene that encodes from 1 to 150 of the peptides identified by Sette et al. The Examiner further notes that Sette et al. provide guidance for creating and constructing polyepitopic compositions such as minigenes, such as selecting epitopes with sequences that meet predetermined criteria for conservancy, in Examples 10 and 11. The Examiner notes that Sette et al. disclose that a minigene expression plasmid typically contain supermotif or motif- bearing epitopes from multiple HPV antigens, preferably including both early stage and late stage antigens, so that multiple supermotifs and motifs are covered to ensure a broad population coverage. The Examiner also notes that Sette et al. disclose in detail a method for constructing minigene-bearing expression plasmids.

The Examiner further notes that Fikes et al. disclose minigene vaccines encoding multiple epitopes, as well methods for creating a DNA sequence encoding selected epitopes for expression in human cells by reverse translating the selected epitopes,

using a human codon usage table to guide the codon choice for each amino acid in the sequence, and then synthesizing corresponding oligonucleotide sequences encoding the plus and minus strands of the minigene which can be subsequently cloned into a desired expression vector. The Examiner also notes that Fikes et al. disclose two methods for functional testing of the minigenes, target cell sensitization, and immunogenicity.

The Examiner notes that Richards discloses the use of isocaudamers, namely Esp3A1 and *Eco*RI, to clone a cDNA into the pSK213 vector twice, once at the *Eco*RI site to include prokaryotic transcription and once at the Esp3A1 site to exclude transcription from occurring in *E. coli*.

The Examiner also notes that that the applicants state that isocaudamers are known in the art, and that they may be used in the practice of the present invention.

The Examiner concludes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to use isocaudamer linkage in the method of either Sette or Fikes for the advantage taught by Richards above. The Examiner states that because of this known advantage, one would be motivated to use the isocaudamer linkage. The Examiner further states that one would have a reasonable expectation of success in obtaining a polyepitopic chimera gene vaccine since the isocaudamer linkage had been used, and is known in the art in making polyepitopic chimeric gene vaccine.

In response to the Examiner's rejection, applicants respectfully point out that the Examiner has not made out a *prima facie* case of obviousness of the presently claimed invention by the citation of these references.

There is nothing in any of the individual references, nor in any combination of the individual references, which would teach, suggest or motivate one of ordinary skill in the art to employ the presently claimed method. In particular, there is no teaching or suggestion that isocaudamer linkages be employed to construct nucleic acid molecules encoding randomly combined bi-epitopes. Further, there is no teaching or suggestion that the nucleic acid molecules encoding bi-epitopes be randomly assembled into polyepitope chimeric genes with different lengths. Nor is there any teaching or suggestion that the resulting polymeric chimeric genes having different lengths be isolated into a plurality of different length ranges, purified, amplified and subcloned into expression vectors to obtain polyepitope chimeric gene expression libraries. Nor is there

any teaching or suggestion that the diversity or immunogenicity of these expression libraries be assessed. Nor is there any disclosure or suggestion the results of screening the expression libraries for diversity and immunogenicity be employed in selecting at least one such expression library for further screening of clones from such expression libraries to identify individual polyepitope gene clones for use as vaccines.

Sette et al., who disclose polyepitope gene vaccines for HPV, actually teach away from the presently claimed invention by the method disclosed in their apparently prophetic Example 11 for constructing minigene multi-epitope DNA plasmids. Sette et al. disclose plasmids including multiple CTL and HTL peptide epitopes, such as HLA-A2 supermotif-bearing epitopes, HLA-A1 motif-bearing epitopes, HLA DR supermotif-bearing epitopes et al. Sette et al. advise including epitopes derived from multiple virial antigens, in order to ensure broad population coverage. However, Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene. Thus, one of ordinary skill in the art would, following the disclosure of Sette et al., construct polyepitope chimeric gene vaccines with no attempt to randomize the sequence of epitopes within the construct, and without any recognition that the sequence could have an effect on the immunogenicity of the construct.

Similarly, Fikes et al. disclose minigene vaccines incorporating multiple epitopes, but fail to disclose any recognition that the sequence of epitopes in the construct may have an effect on immunogenicity. Fikes et al. advise that optimized peptide expression and immunogenicity can be achieved by incorporating introns to facilitate efficient gene expression, and that expression can be increased mRNA stabilization sequences and sequences for replication in mammalian cells (co. 31, lines 35-42). However, Fikes et al. fail to disclose randomizing the sequence of epitopes in the construct and screening for optimized immunogenicity.

Thus, the combination of references cited by the Examiner does not make out a *prima facie* case of obviousness.

Following KSR Intern'l Co. vs. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d 1385 (2007), the Manual of Patent Examining Procedure at ¶ 2141 acknowledges that "[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reasons why the claimed invention would have been obvious...." As summarized in this

portion of the MPEP, various rationales (A-G) may support a conclusion of obviousness. However, none of the listed rationales are applicable to the present situation.

For example, a simple combination of the cited references does not yield the present invention, for the reasons listed above (rationale A). The invention cannot be categorized as a simple substitution of one element from another (rationale B) nor is it merely the use of known techniques to improve similar devices (methods, or products) (rationale C).

Further, the invention does not amount to applying a known technique to a known device (method, or product) ready for proving to yield predictable results (rationale D).

With respect to rationale E, an "obvious to try" standard, the invention cannot be categorized as simply choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

With respect to rationale F, there is no "known work in one field of endeavor" that "may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art".

Finally, with respect to rationale G, this follows the standard "TSM test", requiring some "teaching, suggestion or motivation in the prior art that would have led one of ordinary skill to modify the prior art references or to combine prior art reference teachings to arrive at the claimed invention". Again, since, as detailed above, it is submitted the references fail to disclose many aspects of the present invention, it is not seen how any theoretical combination of them could arrive at the present invention.

Reconsideration and withdrawal of the rejection entered under 35 U.S.C 103 are respectfully requested as applicable to the amended claims for these reasons.

Early reconsideration, withdrawal of all objections and rejections, and allowance of this application are respectfully solicited.